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Cardiovascular risks and brain function: a functional magnetic resonance imaging study of executive function in older adults

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ABSTRACT

Cardiovascular (CV) risk factors, such as hypertension, diabetes, and hyperlipidemia are associated with cognitive impairment and risk of dementia in older adults. However, the mechanisms linking them are not clear. This study aims to investigate the association between aggregate CV risk, assessed by the Framingham general cardiovascular risk profile, and functional brain activation in a group of community-dwelling older adults. Sixty participants (mean age: 64.6 years) from the Brain Health Study, a nested study of the Baltimore Experience Corps Trial, underwent functional magnetic resonance imaging using the Flanker task. We found that participants with higher CV risk had greater task-related activation in the left inferior parietal region, and this increased activation was associated with poorer task performance. Our results provide insights into the neural systems underlying the relationship between CV risk and executive function. Increased activation of the inferior parietal region may offer a pathway through which CV risk increases risk for cognitive impairment.

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1. Introduction

Cardiovascular (CV) risk factors, such as hypertension, diabetes mellitus, dyslipidemia, and obesity, are important modifiable risk factors associated with cognitive impairment and risk of dementia in older adults (Kivipelto et al., 2001; Kloppenborg et al., 2008; Whitmer et al., 2005). CV risk factors are highly prevalent in older adults, and they rarely exist alone. Although each individual CV risk factor can have a deleterious impact on cardiovascular and cognitive health, typically, it is often a combination of several risk factors that act in both an additive and multiplicative manner to impose the greatest risk of cardiovascular diseases and dementia (Kalmijn et al., 2000; Kivipelto et al., 2001; Luchsinger et al., 2005; Whitmer et al., 2005).

Executive functions, such as planning, organizing sequential tasks, inhibiting interfering sources of information, and task switching, are important cognitive functions thought to be not only susceptible to the effects of aging (Buckner, 2004; Head et al., 2004; Hedden and Gabrieli, 2004; Raz et al., 1998; West, 1996) but also impaired in the early stages of dementia and Alzheimer's disease (AD) (Albert et al., 2001; Buckner, 2004; Carlson et al., 2009). Moreover, CV risk factors and cardiovascular diseases (CVD) have been consistently found to be associated with deficits in executive function (Elias et al., 2004; Fontbonne et al., 2001; Garrett et al., 2004). Although the relationship between CV risk factors and cognitive impairment and dementia in older adults is established, the mechanisms linking them are just beginning to be explored. Neuroimaging techniques are one way to investigate possible mechanisms, however few studies have used these techniques to examine the association between individual CV risk factors and functional brain activation (Jennings et al., 2005).

The present study aims to investigate the association between aggregate CV risk assessed by a nationally validated Framingham General Cardiovascular Risk Profile and executive brain function using functional magnetic resonance imaging (fMRI) in a group of community-dwelling older adults who are cognitively normal, yet at elevated risk for cognitive impairment. The executive function task used in this study targets selective attention and inhibitory control of broad executive function and has been shown to be sensitive to the effect of cardiovascular fitness on brain function changes in older adults (Colcombe et al., 2004), and thus might be sensitive to an

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aggregate CV risk score. In the neuroimaging literature, using similar tasks, regions of the frontal and parietal cortices, particularly the middle frontal gyrus and the superior and inferior parietal lobes, are consistently implicated (Casey et al., 2000) and are regions of primary interest here. Whether aggregate CV risk is associated with greater or less task-related activity in attentional circuitry described previously is still under exploration. Nonetheless, fMRI studies in at-risk older adults have often shown more extensive and stronger cortical recruitment in these task-related regions (Bondi et al., 2005; Bookheimer et al., 2000). Hence, we hypothesized that greater aggregate CV risk would be associated with more extensive and greater activation in executive function-related brain regions, particularly frontal and parietal cortices.

2. Methods

2.1. Participants

The study sample for this fMRI study was drawn from the Brain Health Study (BHS), a nested study within the Baltimore Experience Corps Trial (BECT). The BECT is a randomized controlled trial of the Experience Corps (EC) program in Baltimore, a volunteer senior service program in urban elementary schools, initiated in 2006 (Fried et al., 2013). Seven hundred and two eligible participants were recruited and randomized to the EC program intervention or a usual low-activity control group. Eligibility criteria have been described previously (Carlson et al., 2008; Steiger, 1980), and included as: (1) being aged 60 years or older; (2) English speaking; (3) minimum sixth grade reading level on the Wide Range Achievement Test (Wilkinson, 1993); (4) Mini-Mental State Examination (Folstein et al., 1975) score of 24 or higher; and (5) completion of the Trail Making Test (Reitan, 1958) parts A and B within the allocated time (part A = 240 seconds and part B = 360 seconds). The BHS simultaneously recruited 120 of the trial participants before randomization within the BECT, to avoid any potential selection biases associated with knowledge of placement. The BHS was designed to examine the biological mechanisms by which the EC program induces cognitive and brain plasticity, using structural and functional brain magnetic resonance imaging (MRI), and a fasting blood panel of metabolic profiles collected at baseline. Additional eligibility criteria included were: (1) right hand dominance to avoid possible laterality confusion in left-handed individuals; (2) no implanted pacemaker, defibrillator, or other electronic or metal devices; and (3) no history of atrial fibrillation, stroke, brain tumor, brain hemorrhage, or brain surgery for a cerebral aneurysm. The study was approved by the Johns Hopkins Institutional Review Board and all participants provided written and informed consent.

fMRI scans were collected on 113 participants in the BHS. Twenty-four participants were excluded because one or more of the variables needed to calculate the Framingham General Cardiovascular Disease Risk Profile were not available at baseline. In addition, 11 participants above the age of 75 years were excluded because they were outside the age range in which the Framingham General Cardiovascular Disease Risk Profile was developed. Finally, eighteen participants were excluded because of fMRI factors such as poor image quality, artifacts and/or excessive motion. The final sample included 60 participants. Fig. 1 presents the flowchart describing study sample selection.

2.2. Assessment of cardiovascular risk factors

Aggregate CV risk was assessed using a newly-developed Framingham general cardiovascular disease (CVD) risk profile. This risk score is designed for use in primary care to identify individuals at high risk for a broad range of CVD events including coronary heart disease (coronary death, angina, coronary insufficiency), cerebrovascular events (all strokes and transient ischemic attacks), peripheral arterial disease, and heart failure. Its development was based on 1174 CVD events over a 12-year follow-up period for 8491 participants aged 30–74 years in the Framingham Heart study (D'Agostino et al., 2008). The risk profile, calculated using age, sex, high density lipoprotein (HDL) cholesterol, total cholesterol, treated or untreated systolic blood pressure, cigarette smoking, and diabetes, provides an estimate of the risk of CVD over a 10-year period. Though this risk score was developed in a predominantly white population, it has been validated in other racial groups such as African-Americans (Hurley et al., 2010).

Components of the risk profile were drawn from questionnaire and physical examination data at baseline. Systolic blood pressure was taken in the sitting position after resting with the sphygmomanometer. Treated hypertension was determined by self reported history and/or use of antihypertensive medication. Medical history of cardiovascular events was also obtained via self-report. Participants were asked about history of a number of cardiovascular events, including heart attack (or myocardial infarction), congestive heart failure, angina (or chest pain because of heart disease), intermittent claudication (or pain from blockage of the arteries), stroke or brain hemorrhage, and transient ischemic attack. No participants in the present study reported any cardiovascular events described previously. Participants were categorized by their cigarette smoking status as current smokers or past or nonsmokers. Diabetes was defined by self-report of diagnosis of diabetes or by a fasting glucose ≥126 mg/dL. A 10-year risk of incident CVD, expressed as a percentage, was calculated from the Cox model formulas (D'Agostino et al., 2008).

2.3. Executive function task

A modified version of the Eriksen flanker task (Botvinick et al., 1999; Colcombe et al., 2005) was used to measure components of executive function, specifically selective attention and inhibition. This task has been used previously to study executive function in older adults (Colcombe et al., 2004, 2005). Participants were asked to press a button in their left or right hand as quickly and accurately as possible to indicate the direction of a central target arrow flanked by 4 arrows pointing in the same direction (congruent; <<<<<) or in the opposite direction (incongruent; >><>>). Executive demand was manipulated in 2 ways, through the direction of the flanking arrows (i.e., congruency) and a visual cue to help focus attention on the central arrow (small red circle) versus a cue around all 5 arrows that provided no information (large red circle). Therefore, incongruent arrows with a large cue would have the greatest demands on executive function while the congruent arrows with a small cue would have the lowest demands.

This yielded 4 conditions shown in Fig. 2: congruent small circle (ConSm), incongruent small circle (IncSm), congruent large circle (ConLg), and incongruent large circle (IncLg). The participants were presented 40 trials of each condition for a total of 160 trials in a rapid event-related paradigm. Each stimulus was displayed for 2 seconds in the middle of the screen on a black background. The interstimulus interval varied with a 3 second presentation of a central fixation crosshair followed by 40% jittered periods. ISIs ranged from 1.5 seconds to 18.5 seconds, with a mean of 3.7 seconds. All stimuli were presented using E-Prime on an MRI-safe back projection system.

Accuracy and reaction time (RT) were recorded for each trial. A measure of interference (the flanker effect; Eriksen and Eriksen, 1974), representing demand for executive function, was computed as (mean RT of incongruent trials − mean RT of congruent trials) separately by cue size. Only correct responses were analyzed. Two

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